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| 10/552,134 | 09/14/2006 | Irina Velikyan | PH0334 | 7198 |

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| EXAMINER | |
|---|---|
| PERREIRA, MELISSA JEAN | |

| ART UNIT | PAPER NUMBER |
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| 1618 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,134 | VELIKYAN ET AL. | |
| | Examiner | Art Unit | |
| | MELISSA PERREIRA | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,5 and 7-16* is/are pending in the application.

4a) Of the above claim(s) *16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/26/10 has been entered.

2. Claims 1-3,5 and 7-16 are pending in the application. Claim 16 is withdrawn and claims 4 and 6 were canceled in the amendment filed 1/26/10.

### *New Grounds of Objection/Rejection*

### *Claim Objections*

3. Claims 1,5 and 7 are objected to because of the following informalities: they recite, "macrocyclic bifunctional chelating agent", "chelating agent" and "bifunctional chelating agent". Appropriate correction is required for consistency.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. It is unclear what compounds would be encompassed by the terms "a part, a fragment, a derivative or a complex" thus the metes and bounds are not defined as the specification fails to define such "a part, a fragment, a derivative or a complex". Further, such "a part, a fragment, a derivative" are not recognized terms of the art.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3,5 and 7-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (WO03/059397) in view of Yngve (Int. Diss. Abs. **2001**, *62*), Bottcher et al. (US 5,439,863) and Lidström et al. (*Tetrahedron* **2001**, *57*, 9225-9283) and in further view of Maier-Borst et al. (GB 2056471A) and Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, *43*, 1088-1093).

8. Griffiths et al. (WO03/059397) discloses a radiolabeling method for the preparation of a NOTA or DOTA (containing N hard donor atoms) labeled $^{68}$Ga for use in PET (p18, paragraph 1) and the development of a $^{68}$Ge/$^{68}$Ga in-house titanium dioxide generator (p7, paragraph 3; p8). The macrocyclic-chelating agent, such as DOTA may be linked to a peptide that can target the site of a disease, thus generating a

bifunctional chelating agent comprising a targeting vector which will be site-specific (p9, paragraph 1).

9. The method of producing a radiolabeled gallium complex involves reacting the solution of a peptide labeled macrocyclic chelate with the $^{68}$Ga diluted from the $^{68}$Ge/$^{68}$Ga titanium dioxide generator which can be fitted with an anion-exchange membrane, such as a Q5F cartridge (p12, paragraph 1; p13, paragraph 2; p16, paragraph 2). Griffiths et al. teaches that the advantage of the gallium-68 generator of the disclosure is that gallium-68 is eluted without unwanted over-dilution (p16, first full paragraph) where the prior art teaches of gallium-68 eluted from previous generators is present in extremely dilute solution, typically under one picomole per milliCurie (p4, paragraph 3). Griffiths et al. (WO03/059397) does not disclose a $^{68}$Ga-DOTA-oligonucleotide, the synthesis of the $^{68}$Ga-DOTA-peptide complex via microwave, or the anion exchanger comprising $HCO_3^-$ counterions of the instant claims.

10. Yngve (Int. Diss. Abs. **2001**, *62*) discloses the preparation of a phosphorothiolated $^{68}$Ga-DOTA-oligonucleotide and a $^{68}$Ga-DOTA-octreotide for use in PET (p12, paragraph 2; p21, last paragraph; p40, paragraph 2). The production of $^{68}$Ga is from a generator system via an ion-exchange column (p39, paragraph 3). The labeling of octreotide (a synthetic octapeptide that show high selectivity for the somatostatin receptor) has been widely investigated due to the role of somatostatin for tumor diagnosis and treatment. Radiolabeled octreotides are routinely used for clinical applications.

11. Bottcher et al. (US 5,439,863) discloses the preparation of metal complex salts via microwave irradiation (column 3, line 45). The complexes are prepared from metal ions, such as those of the second and third main group, not excluding gallium and multitoothed chelating ligands that occupy more than one coordination site on the central metal atom (column 3, lines 55-59; column 4, lines 44-46). The ligands of the disclosure may include those with dioxime (N and O containing), etc. groups (column 5, lines 20-24). The use of microwave as the high-energy input allows for a continuous conversion, single-stage reaction with short reaction time (i.e. a few minutes) and ease of separation of the formed complexes (column 4, line 19; column 5, lines 56+; column 6, lines 1-5; claim 4).

12. Lidström et al. (*Tetrahedron* **2001**, *57*, 9225-9283) discloses that microwave technology has been used since the late 1970s for inorganic chemistry and 1980s for organic synthesis. The shorter reaction times are the main advantage of the microwave technique as microwave heating can be very rapid, producing heat profiles not easily accessible by other heating techniques (p9226, paragraph 2; p9231, third full paragraph). The microwave technique can provide 100 W (figure 10) and a metal-macrocyclic chelate complex may be generated via the microwave technique (5.11 Organometallic reactions p9267, last entry).

13. Maier-Borst et al. (GB 2056471A) discloses the separation of $^{68}Ga$ from its parent nuclide with water via passing the eluant from a generator column into an anion exchanger comprising quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene and washing the anion exchanger with water (p4, lines 44-48).

14. Wheaton et al. (*Industrial and Engineering Chemistry* **1951**, *43*, 1088-1093) discloses strongly basic anion exchange resins which are quaternary ammonium salts having a polystyrene crosslinked with divinylbenzene base (Dowex 1 and 2) (p1088, paragraph 1). Dowex 1 and 2 are provided in various forms, such as bicarbonate (tables I and II).

15. At the time of the invention it would have been obvious to produce a $^{68}$Ga-DOTA-oligonucleotide complex, such as that of Yngve for use as a PET tracer via the production of $^{68}$Ga from a $^{68}$Ge/$^{68}$Ga titanium dioxide generator as disclosed by Griffiths et al. Griffiths et al. teaches that the titanium dioxide generator produces gallium-68 that is more concentrated (i.e. nanomolar, micromolar) than one picomole per milliCurie of the prior art.

16. Griffiths et al. teaches of the conjugation of $^{68}$Ga-DOTA to peptides and therefore, it is obvious to those skilled in the art to make known substitutions on compounds that are similar in structure and function, such as the oligonucleotides of Yngve for the peptides of Griffiths et al. to observe the effects on the function of such compounds and to use the observations/data to further manipulate a compound to generate the desired effect, such as sites-specific targeting of the complexes to somatostatin for tumor diagnosis and treatment.

17. The microwave synthesis technique for the method of producing metal-chelate complexes was known by Bottcher et al. and Lidström et al. at the time of the invention. Therefore, it would have been obvious to one skilled in the art to utilize the microwave acceleration technique for a faster and more reproducible preparation of the $^{68}$Ga-

DOTA-oligonucleotide complex, such as that of the combined references of Griffiths et al. and Yngve to generate a complex useful in the treatment or diagnosis of tumors with minimal side product formation. Microwave acceleration techniques have been utilized since the 1980's in a number of production methods for radioactive precursors and radiotracers labeled with positron-emitting nuclides. The microwave method is mostly associated with shortened reaction times and encompasses the microwave conditions of the instant claims (Lidström et al.). Since the microwave technique was known in the art to reduce reaction times of organometallic reactions, such as metal-chelate complexes, one would have a reasonable expectation of success for preparing radiotracer via labeling reactions with this improved microwave technique.

18. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute an anion exchanger, such as that of Maier-Borst et al., which does not require a chelating agent (i.e. EDTA) for separation, for the anion exchanger of Griffiths et al. to separate $^{68}$Ga from its parent nuclide. The disadvantage of forming a $^{68}$Ga-EDTA complex via addition of a chelating agent (i.e. EDTA) to elute $^{68}$Ga from a metal oxide exchanger was known in the prior art and requires the destruction of the $^{68}$Ga-EDTA complex before further processing to obtain radiopharmaceutical agents which is both time-consuming and expensive (see Maier-Borst et al. p1, lines 10-16). Also, at the time of the invention it would have been obvious that the anion exchange resin comprising quaternary ammonium groups incorporated in the matrix of styrene and divinylbenzene (Maier-Borst et al.) may comprise the bicarbonate counterion as the

bicarbonate provides for a minimal amount of swelling and thus greater selectivity of the anion exchange resin (Wheaton et al. p1089, resin swelling).

***Response to Arguments***

19. Applicant's arguments filed 1/26/10 have been fully considered but they are not persuasive.

20. Applicant asserts that Bottcher et al. concerns non-radioactive metal complexes as "latent polymerization catalysts" and uses macroscopic, in fact molar amounts (1 to 2 moles) of metal ion in examples 1 to 4 therein, and envisages that the metal complexes would precipitate as crystals. Such macroscopic scale, indeed crystallization, represents completely different chemistry to the high dilution solutions employed with the radioisotopes of the present invention. Thus applicants contend that the person skilled in the art would know that such radiometal complexes are rarely if ever handled in macroscopic amounts, but instead used in microscopic chemical quantities in solution. The radioactive gallium complexes are typically prepared in nanomolar amounts.

21. The instant claims do not recite amounts/concentrations of the reagents. The reference of Bottcher et al. was not used to teach of the amounts/concentrations of the reagents for the synthesis of the metal complexes of the disclosure but was used to teach that microwave irradiation was known at the time of the instant invention for the preparation of metal complex salts for its advantages, such as continuous conversion,

single-stage reaction with short reaction time and ease of separation of the formed complexes.

22. The reference of Lidström et al. was also used to teach of that microwave irradiation was known at the time of the instant invention for organometallic synthesis for its advantage of reduced reaction times.

23. Since the microwave technique was known in the art to reduce reaction times of organometallic reactions, such as metal-chelate complexes, one would have a reasonable expectation of success for preparing radiotracer via labeling reactions with this improved microwave technique.

24. Applicant asserts that the instant invention deals with macromolecular bioconjugates, i.e. "bifunctional chelates". Bottcher et al. does not teach, disclose, or suggest the use of macromolecular bioconjugates. Unlike the present invention, Bottcher et al. studies the preparation of metal complex salts of second and third group metals and multidentate chelating agents. The instant application, however, focuses on gallium radioisotopes [as Ga(III)] complexation with macrocyclic chelators-particularly conjugated to "targeting vectors". Applicant contends that the person skilled in the art would know that such vectors are typically expected to be particularly sensitive to radiolysis and hence would simply be unsuitable for the robust chemical conditions taught by Bottcher et al. Thus, Bottcher et al. and Griffiths et al. are in very different fields of endeavor.

25. Bottcher et al. was not used to teach of gallium radioisotopes complexation but was used to teach of the microwave technique to reduce the reaction times for the

production of metal complex salts comprising a metal salt of the second and third main groups (not excluding gallium) and a ligand (Bottcher et al. column 2, lines 20-58) in substantially quantitative yield and high purity. The chelating ligand, L, (multidentate chelating agents) may comprise all organic compounds which have at least two atom groupings with free electron pairs or electron gaps for forming complex compounds (Bottcher et al. column 5, lines 20-23). Therefore, the chelating ligand (multidentate chelating agents) of the disclosure encompasses the bifunctional chelates of the instant claims.

26. Lidström et al. further teaches that the microwave technique was known at the time of the invention to provide for shorter reaction times for organometallic reactions as microwave heating can be very rapid, producing heat profiles not easily accessible by other heating techniques.

27. It would have been obvious to one ordinarily skilled in the art to utilize the microwave techniques of Bottcher et al. and Lidström et al. for the $^{68}$Ga-DOTA complexes of Griffiths et al. to provide for substantially quantitative yield and high purity of metal-multidentate ligand complexes while reducing reaction times.

28. Applicant asserts that there is not teaching in Bottcher et al. of successfully applying microwave activation in coordination chemistry.

29. Bottcher et al. teaches that the metal salt and the chelating ligand are mixed together, brought to the desired temperature and then the high energy input can take place through microwave, etc. In this way, the time the reaction mixture spends in the

reactor can be reduced to a few minutes (Bottcher et al. column 5, lines 56+; claim 4). The use of microwave activation does not need to be exemplified.

30. Applicant asserts that Bottcher et al. is silent on the specific microwave conditions of present, revised claim 1- where the irradiation power and time are specified.

31. The reference of Bottcher et al. was not used to teach of the microwave power (W) conditions but teaches that the reaction time can be reduced to a few minutes, such as 2 minutes which encompasses the microwave time conditions of the instant claims.

32. Lidström et al. teaches that the microwave technique can provide 100 W (Lidström et al. figure 10) which encompasses the microwave power conditions of the instant claims.

33. Applicant asserts that Yngve et al. describes the preparation of $^{68}$Ga-DOTA-oligonucleotide complexes, where $^{68}$Ga is obtained via an ion exchange column. Yngve et al. is, however, silent on microwave irradiation and cannot therefore remedy the deficiencies of Griffiths et al. and Bottcher et al. and/or Maier-Borst et al.

34. Yngve et al. was used to teach of the conjugation of $^{68}$Ga-DOTA to oligonucleotides for the site-specific targeting of the complexes to somatostatin for tumor diagnosis and treatment and was not used to teach of the preparation of $^{68}$Ga.

***Double Patenting***

35. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

36. Claims 1-3,5 and 7-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2 and 6-14 of copending Application No. 10/522,206. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of producing a radiolabeled gallium complex of the instant claims encompasses the method for producing a $^{68}$Ga-radiolabeled complex of copending Application No. 10/552,206. Both inventions involve reacting a $^{68}$Ga radioisotope with a bifunctional chelating agent

comprising a targeting vector (i.e. peptide or oligonucleotide) under microwave conditions. The microwave technique of copending Application No. 10/552,206 encompasses the microwave conditions of the instant claims (not excluding 80-120 W for 20s to 2 min). The inventions also include the same peptide or oligonucleotide targeting moiety that may be bound to the chelating agent for site-directed localization. The generation of the $^{68}$Ga radioisotope of both applications involves eluting the $^{68}$Ga from a $^{68}$Ge/$^{68}$Ga titanium dioxide generator followed by purification of the $^{68}$Ga eluate via a strong anion exchanger comprising $HCO_3^-$ counterions. Therefore, the resulting radiolabeled gallium complex of the instant claims is obviously generated via the synthesis and isolated and would encompass that radiolabeled gallium complex of the copending application.

37. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

38. Claims 1-3,5,7-13 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3,7-15 of copending Application No. 11/358,681. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of producing a radiolabeled gallium complex of the of the instant claims encompasses the method for labeling synthesis of radiolabeled gallium complex of copending Application No. 11/358,681. Both inventions involve reacting a $^{68}$Ga radioisotope with a bifunctional chelating agent comprising a peptide using the same microwave conditions. The

inventions also include a targeting moiety that may be bound to the chelating agent for site-directed localization. The generation of the $^{68}Ga$ radioisotope of both applications involves eluting the $^{68}Ga$ from a $^{68}Ge/^{68}Ga$ titanium dioxide generator followed by purification of the $^{68}Ga$ eluate via a strong anion exchanger comprising $HCO_3^-$ counterions. Therefore, the resulting radiolabeled gallium complex of the instant claims is obviously generated via the synthesis and isolated and would encompass that radiolabeled gallium complex of the copending application.

***Conclusion***

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
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/Melissa Perreira/
Examiner, Art Unit 1618